Letter to the Editor

rare tumors

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Nirogacestat and its potential impact on desmoid tumor

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Dear Editor,

Desmoid tumors (DT) are rare, benign, and invasive soft tissue tumors affecting 3–5 people in one million each year. Also known as desmoid fibromatosis, they present usually in the second and fourth decade of life, with an unpredictable prognosis and a risk of significant impairment in quality of life. According to estimates there are 1000 to 1650 new diagnoses in the United States each year.[1] Habitually, these tumors are found in the abdomen, arms, and legs, however, they can affect vital organs as well. Desmoid tumors do not metastasize but painful disfigurement and problems in functioning due to local, aggressive growth can occur.[2] Since desmoid tumors lack the ability to metastasize, local control using surgery and radiation has traditionally been the mainstay of therapy for these tumors. However, recurrence rate is very high, especially after surgery and in rare cases, it can be fatal.[2] Therefore, the need for effective treatment is undeniable.

The Food and Drug Administration (FDA) recently awarded Nirogacestat's new drug application (NDA) for the treatment of adult patients with desmoid tumours a priority evaluation.[3] The FDA has also given desmoid tumours in adult patients Fast Track and Breakthrough Therapy classifications.[3] Nirogacestat is an oral, specific, small-molecule gamma secretase inhibitor that works by cleaving a variety of transmembrane protein complexes, including Notch, which may be involved in pathways that support the development of desmoid tumours.[4] Inhibition of γ-secretase preserves membrane-bound B-cell maturation antigen (BCMA) and increases target density by reducing the levels of soluble BCMA, thus serving as a decoy receptor for BCMA-targeted therapy.[4] The ability of Nirogacestat to potentiate the activity of BCMA-targeted therapy has been observed in preclinical models of multiple myeloma.[4]

A DeFi study, the largest and most rigorous randomized controlled trial was conducted in which 142 patients with advanced desmoid tumors were recruited.[5] Patients were randomized to receive either Nirogacestat 150 mg or placebo twice daily in cycles of 28 days until they developed symptoms on radiologic imaging.[5] The results showed a statistically significant improvement in progression of survival in patients randomized to Nirogacestat compared to placebo, with an average 71% reduction in risk of disease advancement.[5] Participants taking Nirogacestat improved by 41% in their response within 5.6 months, compared to 8% in a longer period of 11.1 months by the placebo group.[5]

However, treatment was stopped due to ovarian dysfunction, which is defined by investigator-reported events of amenorrhea, premature menopause, menopause, and ovarian failure and was seen in 75% of women of childbearing potential receiving Nirogacestat. Nirogacestat demonstrated a manageable safety profile in DeFi studies, with 95% of all treatment-emergent adverse events.[6] Therefore, treatment should be individualized for each patient to optimize tumor control and improve symptom burden, including impact on pain, physical function and overall quality of life. It may become the standard of care for patients with desmoid tumors who require systemic treatment despite the high rate of ovarian failure as it has a moderate safety profile.[6] Nevertheless, the potential risks associated with the drug must be carefully monitored to ensure its safety for patients.

Nirogacestat may enhance patients' quality of life and offer hope to individuals who are suffering from the condition. The FDA's approval of Nirogacestat represents an

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important turning point in the continuing fight against Desmoid tumors. Surgery has long been the main form of therapy for desmoid tumors, with newer approaches being more cautious and less aggressive than those previously practiced.[7] However, due to high rates of local recurrences and subpar functional results, surgery has caused a move towards nonsurgical approaches.

Non-steroidal anti-inflammatory medicines (NSAIDS) are often used as medical treatments, although their mechanisms of action in treating desmoid tumors are not well known.[7] As the tumor has a tendency to spontaneously retreat, it is difficult to determine any meaningful benefits. Standard chemotherapy sessions employ anthracycline-based regimens, which are associated with a response rate of around 50%, but they have also been linked to substantial heart damage.[7] The safety profile of Nirogacestat will ultimately determine if it can revolutionize the way desmoid cancers are treated.[7] Thus, it is crucial to keep funding research towards the creation of novel medications like Nirogacestat. Nirogacestat's FDA clearance is a laudable accomplishment that highlights the unwavering dedication of researchers and medical experts to finding viable therapies for desmoid tumors.

Author contributions

Dr Samia Rohail researched literature and conceived the study. Dr Muskan Asim Taimuri and Dr Alishba Adnan were involved in protocol development, gaining ethical approval, patient recruitment and data analysis.

Authors note

Dr Areeba Fareed wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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